DRAFT

INTERACTION PROFILE FOR: ATRAZINE, DEETHYLATRAZINE, DIAZINON, NITRATE, AND SIMAZINE

Prepared by:

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Public Health Service
Agency for Toxic Substances and Disease Registry

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PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

The public comment period ends March 31, 2005. Comments should be sent to:

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

Dale Hattis, Ph. D.
The George Perkins Marsh Institute
Center for Toxicology, Environment, and Development
Clark University
Worcester, MA

Kannan Krishnan, Ph. D.
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All reviewers were selected in conformity with the conditions for peer review specified in CERCLA Section 104(I)(13).

Scientists from ATSDR have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

Atrazine, deethylatrazine, simazine, diazinon, and nitrate were chosen as the subject mixture for this interaction profile because they frequently occur together in rural well water. Atrazine and simazine are triazine herbicides, deethylatrazine is a metabolite and an environmental degradation product of atrazine and other triazine herbicides, diazinon is an organophosphorus insecticide, and nitrate is a common contaminant resulting from fertilizers and human and animal waste. The exposures of greatest concern for this mixture in rural well water are intermediate and chronic oral exposures. No pertinent health effects data or physiologically-based pharmacokinetic (PBPK) models were located for the complete mixture. Therefore, the exposure-based screening assessment of potential health hazards for this mixture depends on an evaluation of the health effects and mechanistic data for the individual components and on the joint toxic action and mechanistic data for various combinations of the components. This profile discusses and evaluates the evidence for joint toxic action among atrazine, deethylatrazine, simazine, diazinon, and nitrate. The profile also discusses how public health assessments can incorporate concerns about interactions, additivity, and potential human exposures to mixtures of these chemicals.

Effects of concern for this mixture include reproductive effects (atrazine, deethylatrazine, and simazine), neurological effects (diazinon), and hematological effects (nitrate). Although none of the components has been classified as a carcinogen, atrazine and simazine can react with nitrite (nitrate metabolite) in the environment and *in vivo* to form N-nitrosoatrazine and N-nitrososimazine. Structure-activity considerations raise a concern for potential carcinogenicity of these nitrosamines.

To screen the mixture of atrazine, deethylatrazine, simazine, diazinon, and nitrate for potential hazards to public health, the hazard quotients (ratios of exposures to health guidance values) are estimated for the individual components. If only one or if none of the components has a hazard quotient that is at least 0.1, no further assessment of the *joint toxic action* is needed because additivity and/or interactions are unlikely to result in significant health hazard. If the hazard quotients for two or more of the mixture components equal or exceed 0.1, the following procedures are recommended. To screen this mixture for potential reproductive health hazard, an endpoint-specific hazard index for reproductive effects should be estimated for atrazine, deethylatrazine, and simazine (the triazine components of the mixture). The weight-of-evidence (WOE) analysis for interactions among these components indicates high confidence in the additivity assumption that is the basis for the hazard index. The potential effect of diazinon and nitrate on the reproductive toxicity of these triazines is uncertain. Separate hazard quotients are recommended to screen for the neurotoxicity of diazinon and the hematological toxicity of nitrate. The WOE analysis

indicates that because the triazine components may potentiate the neurologic toxicity of diazinon, the hazard quotient for diazinon may tend to underestimate the hazard of exposure to diazinon when these triazine components are present. Confidence in these predictions is medium. No information regarding the impact of interactions on the hematological toxicity of nitrate was available, so uncertainty regarding the impact of the other components on this effect of nitrate is high.

The interactions of atrazine and simazine with nitrite can result in the formation of N-nitrosoatrazine and N-nitrososimazine, which are more genotoxic than the parent triazine compounds. The WOE analysis predicts an increase in carcinogenic potential. Confidence in this prediction is medium; although adequate data are lacking for these specific compounds, data on other N-nitrosamines and their precursors support this conclusion. Further exposure-based screening for cancer risk is precluded by the lack of suitable data for N-nitrosoatrazine and N-nitrososimazine.

If the reproductive hazard index for the triazines or the hazard quotient for nitrate is greater than 1, or if the hazard quotient for diazinon is close to or above 1, then further evaluation is needed (ATSDR 2001a), using biomedical judgment and community-specific health outcome data. Community health concerns (ATSDR 1992) and the potential for carcinogenicity due to nitrosamine formation should be considered in further evaluations.

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ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
CAS	Chemical Abstracts Service
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
CHO	Chinese hamster ovary
DACT	diaminochlorotriazine
DT	Division of Toxicology
EC_{50}	median effective concentration (produces desired effect in 50% of population)
EPA	Environmental Protection Agency
FQPA	Food Quality Protection Act
GnRh	gonadotropin releasing hormone
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LC_{50}	median lethal concentration (produces desired effect in 50% of the population)
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
mg	milligram
mM	millimole
MRL	Minimal Risk Level
NADH	nicotinamide adenine dinucleotide phosphate
ng	nanogram
NOAEL	no-observed-adverse-effect level
NRC	Nuclear Regulatory Commission
NTP	National Toxicology Program
PAD	population adjusted dose
2-PAM	pralidoxime
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic/ pharmacodynamic
ppb	parts per billion
RfC	reference concentration
RfD	reference dose transaminase
SMR	standardized mortality ratio
TTD	target-organ toxicity dose
µg	microgram
µmole	micromole
U.S.	United States
VOC	volatile organic compound
WOE	weight-of-evidence
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to